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The long-term efficacy and safety of two different corticosteroids in chronic sarcoidosis

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Deflazacort (DFZ) is claimed to have fewer adverse bone effects than prednisone (PDN) at doses with equivalent anti-inflammatory activity (5 mg PDN=6 mg DFZ). However, its safety over the long-term has never been tested in a controlled trial.

The aim of the present study was to assess prospectively the safety and efficacy of DFZ compared with PDN in previously untreated patients with chronic, histologically proven sarcoidosis needing long-term ($\geq$2 yr) corticosteroid therapy.

Thirty-six patients were treated with PDN for 32 ± 18 months and 36 patients were treated with DFZ for 42 ± 18 months, and followed-up with periodic chest X-ray, ^{67}Gallium lung scan, angiotensin converting enzyme (ACE), serum and urinary calcium levels, spirometry, alveolar diffusion (*D*LCO) arterial oxygen tension (PaO_2), bone mineral content (BMC) (by computed tomography), and a complete biochemical and haematological profile. The two groups were similar as regards sex, age, pulmonary and extrapulmonary involvement, parameters of activity and impairment, and initial BMC. Daily starting doses were 23·2 ± 11·4 mg DFZ and 22·3 ± 6·9 mg PDN.

One year of trial was completed by 69 patients, 2 yr by 59 patients, 3 yr by 46 patients and 4 yr by 24 patients. Some patients were followed-up for 5–7 yr. The mean daily dose over the whole period was 15 ± 10 mg DFZ and 10 ± 6 PDN, starting from 21 ± 9 and 15 ± 8 mg in the first year, and progressively declining to a mean of 9 ± 6 mg in both groups in the fourth year. Chest X-ray, ^{67}Ga score, ACE and forced vital capacity improved significantly in both groups. Urine total calcium improved significantly in the PDN group (345 ± 27 to 186 ± 47; $P<0·05$) with a similar but non-significant pattern in the DFZ group (270 ± 28 to 207 ± 39). Non-significant improvements were observed in *D*LCO, PaO_2 and forced expiratory volume in 1 s in both groups.

Drug-related adverse events were more frequent in the PDN group, causing discontinuation of the drug in four PDN patients. Body weight increased mainly in the PDN group [69·9 ± 0·4 to 73·6 ± 0·8 kg *vs* 70·1 ± 0·4 to 70·0 ± 0·6 kg in the DFZ group ($P<0·01$)]. Bone mineral content dropped under the fracture threshold in most PDN patients, who thus appeared at higher risk for fractures. In fact, six atraumatic skeletal fractures were observed in this group but only one in the DFZ group. Two further patients in the DFZ group and eight in the PDN group were obliged to start corrective measures for bone loss and/or bone pain. At the end of the study, 21 patients (12 DFZ, nine PDN) no longer needed corticosteroids, and the others were taking a maintenance daily dose that controlled the disease adequately.

In conclusion, DFZ appeared as effective as PDN in the long-term treatment of chronic sarcoidosis, and it may have fewer side-effects, especially on bone.

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Introduction

Sarcoidosis is a systemic inflammatory disorder of unknown aetiology characterized by granulomas in

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various organs. Although the clinical characteristics and pathology are well defined, the optimal therapy remains unclear and unspecific. Corticosteroids are generally considered beneficial although there is no single criterion for establishing the indications and duration of treatment, the maximal effective dose, or even the real effect of therapy on the natural history of the disease. Furthermore, the long-term use of these drugs may result in significant adverse events, osteoporosis being the most disabling.

Deflazacort (DFZ), a methyl-oxazoline derivative of prednisolone, has been claimed to have anti-inflammatory activity comparable to prednisone (PDN), with less deleterious effect on the bone calcium metabolism, as evaluated in five long-term controlled trials with dual photon absorptiometry measurements of the lumbar spine (1–4), and histomorphometric measurements of bone biopsy at the iliac crest (5). Three double-blind trials were carried out on homogeneous populations of patients with rheumatoid arthritis (2), juvenile chronic arthritis (3) and nephrotic syndrome (4). Two single-blind trials were carried out in less homogeneous groups of patients with sarcoidosis, collagen diseases, asthma and other immune-mediated diseases (1,5). All these trials lasted for at least 1 yr, some patients being studied for up to 18 months. In another controlled double-blind trial, patients with chronic inflammatory disorders were followed-up for 3 months; DFZ, at doses with the same anti-inflammatory activity as PDN, had fewer adverse effects on calcium and cortisol levels (6). All these trials provided ample information on the bone variables but scanty data on the long-term safety of DFZ compared to PDN.

In an uncontrolled study on 40 patients followed-up for 1–5 yr, DFZ was a good and safe approach for the long-term therapy of sarcoidosis (7). In another controlled trial lasting 6 months, DFZ was found to be as useful as PDN in suppressing sarcoid activity (8).

In 1987, the present trial was started with the aim of comparing the long-term efficacy and safety of DFZ and PDN in chronic sarcoidosis requiring long-term corticosteroid therapy. The major end-point was to evaluate the reduction in bone mass and the increase in fractures in those steroid-treated patients.

Methods

STUDY DESIGN

For the requirements of statistical evaluation (see later), 72 patients were needed. Accordingly, all patients satisfying the following admission criteria were eligible:

(1) Histologically proven chronic sarcoidosis:
(2) Need for long-term corticosteroid therapy;
(3) No previous corticosteroid therapy;
(4) Bone mineral content (BMC) not lower than 2 SD below the average reference value (z-score -2 or less); and
(5) No diseases affecting bone metabolism.

Pulmonary sarcoidosis clears without therapy in over 50% of patients within 2 yr, but patients with chronic disease were chosen for study, in whom this probability is very low (see Table 1). The authors' criteria for long-term therapy have been outlined in a previous paper (9). Briefly, corticosteroid therapy is started when there is clinical evidence of both sarcoid activity and functional impairment. A number of markers are taken into consideration according to clinical appropriateness, such as angiotensin converting enzyme (ACE), ^{67}Ga uptake (total body), lymphocyte alveolitis >14% in bronchoalveolar lavage fluid, 10% or more reduction from previous values in vital capacity or 15% or more in alveolar diffusion (D_LCO), increasing dyspnoea or cough, worsening chest X-ray, extrapulmonary disease such as uveitis, lupus pernio, hypercalcemia, hypercalciuria, myocardial disease or others.

PATIENTS

Between 1987 and 1992, 356 new patients with histologically proven sarcoidosis were seen by the authors; 116 needed long-term corticosteroid therapy, many of them after a period of observation without therapy, but 33 were excluded because they were already under treatment, or had been treated with corticosteroids before reaching the authors' Sarcoid Clinic. Fifteen further patients were excluded because their z-score was -2 or less. Most of the 48 patients excluded were treated with DFZ and have already been described in a previous paper (7).

Sixty-eight patients satisfied the admission criteria for the present trial. Four more meeting these admission criteria had already been in follow-up at the Clinic since before 1987, but the indication for corticosteroid therapy had arisen only in 1987 or later. These 72 patients all gave informed consent and were enrolled and allocated at random to PDN (36 patients) or DFZ (36 patients). They form the basis of the present report. The study was scheduled to last at least 24 months. Since enrolment took 5 yr, some patients had been followed-up for up to 7 yr when the trial was closed in December 1994.

As already stated (7,9), the authors do not believe in a rigid protocol because starting dose, subsequent doses and time of therapy must be adapted to each individual clinical situation. For this reason, the

TABLE 1. Baseline characteristics of patients at recruitment

	Deflazacort	Prednisone
n	36	36
Sex	16 F/20 M	17 F/19 M
Postmenopausal	8	6
Age, years*	40·0 ± 11·5	40·8 ± 11·0
Sarcoidosis involvement		
Pulmonary only	17	18
Pulmonary and extrapulmonary	17	15
Extrapulmonary only	2	3
Disease duration, years*	5·6 ± 4·7	3·5 ± 4·6
Course of disease at recruitment		
Steady	6	5
Worsening	24	25
Recent evaluation†	6	6
VCMC, mg k_2HPO_4 ml^{-1}		
Estimated value‡	130·0 ± 4·8	129·8 ± 5·6

*Mean ± SD.
†Too few data in the patient history to understand whether the course is steady, worsening or improving.
‡Mean ± SE (n=58 patients available for the long-term bone study: 30 deflazacort, 28 prednisone).

study was not performed under blind conditions. In most cases, the starting dose was 12·5–40 mg PDN daily, or 15–48 mg DFZ. Maintenance doses and duration of corticosteroid therapy were tailored to the individual clinical need, on the basis of frequent visits to the Sarcoid Clinic, at least once every 2 months in the first year and at least every 4 months thereafter. During these visits, symptoms, compliance with the treatment and side-effects of therapy were evaluated, and a physical examination was done; suggestions were given about the next dose of therapy and the next work-up.

No other drugs known to affect bone metabolism were allowed. Whenever severe bone loss was developing or fractures occurred, corrective and preventive drug strategies were set up (e.g. oestrogens, calcitonin, diphosphonates, etc.). From that moment onwards, the patient receiving these drugs was no longer evaluable for bone toxicity analysis.

DISEASE ACTIVITY AND LUNG FUNCTION MARKERS

The work-up included periodic checks of the criteria for sarcoid activity and functional impairment to assess the efficacy of the drugs, and a biochemical and haematological profile plus periodic bone mineral content evaluation to assess their safety. Chest X-rays were taken in the postero-anterior projection and were classified according to the radiographic stage: Stage 0 was a normal chest film; Stage I had hilar adenopathy alone; Stage II had hilar adenopathy and parenchymal infiltrates, and Stage III had parenchymal infiltrates only. ^{67}Gallium lung scan, based on the uptake of ^{67}Ga, was assessed by a subjective method, using a 0–3 score as described previously (10). Serum ACE was measured by a radiometric method (11); normal values in the authors' laboratory are 34–125 U l^{-1}. Serum and urine calcium levels were followed to gain further information on the disease activity in a study whose primary focus was on bone.

Pulmonary function tests consisted of standard spirometry [forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1)] and the diffusing capacity of the lungs for carbon monoxide (D_LCO); gas analysis of an arterial sample was carried out when low FVC or D_LCO raised doubt about low PaO_2. Techniques and normal values have been described previously (12).

Chest radiography, lung function and disease activity markers were assessed at least every 4–6 months in the first year and from 6 months to 1 yr thereafter; some patients had more frequent controls according to clinical needs.

SAFETY

Safety was assessed on the basis of a biochemical profile including urea nitrogen, creatinine, aspartate and alanine aminotransferases, glutamyltransferase, total proteins and protein fractions, sodium, potassium, bilirubin and urinanalysis; the haematological profile included haemoglobin, haematocrit, red and white blood cell counts, differential count and platelets. All these markers were measured at recruitment and then at least once a year according to clinical needs. Body weight and systolic and diastolic blood pressure were recorded at each visit.

Steroid wasting effects on bone were assessed by measuring trabecular bone mineral density of the lumbar spine by single energy QCT with a Siemens Somaton 2CT Scanner (with antropomorphic calibration phantom), as described previously (13). Vertebral cancellous mineral content (VCMC) was scheduled to be measured yearly, at least three times during the trial: at enrolment, and after 1 and 2 yr. Since enrolment lasted 5 yr, some patients had had more than three QCT assessments (up to eight) when the study was closed in December 1994.

The assessment of fracture events was based on the periodical (6-monthly) radiological examination of the ribs and thoracic spine, and also according to necessity. Radiographs were examined separately by two experienced readers (blinded to the clinical history). The definition of vertebral fracture, as opposed to vertebral deformity, remains controversial (14–16). Bearing in mind the doubts raised by Kleerekoper (14), a vertebral fracture was defined as a reduction of at least 15%, or an absolute decrease of at least 4 mm, on a lateral spine film, in the anterior, middle or posterior height of any vertebral body between baseline and follow-up (16,17). Only new deformities of vertebrae considered to be normal in the initial radiograph were counted as incident fractures (17). Wedge fractures were defined by anterior height reduction, and crush fractures by posterior height reduction (17).

STATISTICS

The required sample size was computed by considering bone mineral loss as *primary variable*. For prefixed risks of type I equal to 0·05, 26 patients per group are sufficient to detect a *true* between-drugs difference in bone loss per year equal to or higher than one standard deviation of individual bone loss per year, with a test power of 95% or more. Since a large number of drop-outs and protocol violations were expected, a sample size of 36 patients per group was chosen.

Between treatment-groups differences in basal conditions of categorical variables (such as sex, menopausal status, disease involvement and duration) were tested by Fisher's exact test (18,19). The time course profiles of safety and efficacy markers were fitted by an ANOVA model for parallel group design with repeated measures (20). Since only a few observations were made after the fourth year of therapy, the analysis was limited to the first 4 yr.

The following null hypotheses were tested: no difference between treatment-groups in basal values; no difference in trend and quadratic departure from linearity between treatment-groups; and no trend and quadratic departure from linearity within either treatment group.

Profiles of safety and efficacy data were reported as *least-squares means* (± SE) (21), based on the model and thus adjusted for the confounding effects of missing data. Bone wasting effects were expressed as VCMC loss (mg K_2HPO_4 ml^{-1}) yr^{-1}. This was estimated from the whole profile of three or more QCT assessments per patient by means of the following linear model:

$$y_i(t)=a_i+\beta_i \times \log_e(t+1)+\varepsilon_i(t)$$

where $y_i(t)$ is the VCMC recorded at time t (months) on the ith patient, constants a_i and β_i are the intercept and the slope (i.e. VCMC loss rate) of the above function for the ith patient, and $\varepsilon_i(t)$ is the random term (biological and technical variability) associated with $y_i(t)$. The average VCMC loss curves for DFZ and PDN were obtained as *mean-constant* (a, β) curves from the individual curves. The first derivative of *mean-constant* curves

$$\partial y(t)/\partial t = \beta/(t+1)$$

provides an expression for VCMC loss velocity.

Goodness of fit of the above model was evaluated by analysis of residuals (observed value-predicted value) (22). The *estimated* VCMC loss takes into account all QCT assessments; thus, it is expected to be somewhat more reliable and precise than the loss *computed* as the difference between the basal and the last QCT assessments.

Data management and analysis were carried out using the SAS® statistical analysis system (Version 6.03) (23).

Results

The baseline characteristics of the 72 patients are outlined in Table 1. There were no significant

TABLE 2. Extrapulmonary sarcoidosis requiring therapy

	Deflazacort	Prednisone
n	19	18
Liver	5	7
Skin	5	4
Heart	2	2
Renal stone	4	4
Hypercalciuria >400 mg per 24 h (without stone)	3	6
Uveitis	4	1
Bone	2	0
Central nervous system	2	0
Spleen	2	1
Joints	1	1
Coexisting pulmonary impairment	17	15

Localizations (peripheral lymphnodes or mild skin lesions) not requiring therapy are not indicated.

differences between the two groups as regards age, sex, disease duration or course at recruitment, or initial VCMC, although disease duration was somewhat less in the PDN group. VCMC refers only to the 58 patients (30 DFZ, 28 PDN) available for the long-term bone study (see later), but the values were nearly the same when considering all 72 patients.

Extrapulmonary involvement requiring therapy was observed in 37 patients, 19 in the DFZ group and 18 in the PDN group (Table 2). In all but five, the extrapulmonary involvement was associated with pulmonary impairment, also requiring therapy. There were nine cases of lupus pernio, four of arrhythmias, one of hemiparesis, one of seizures plus bilateral optic nerve atrophy, and three of hypersplenism.

Table 3 shows the disease markers at recruitment; as expected, chest X-ray was Stage II or III in the majority of cases. There were no differences between the two groups, although the 24-h calciuria appeared higher ($P=0{\cdot}08$) in the PDN group.

TABLE 3. Disease markers at recruitment

	Deflazacort	Prednisone	*P*
Chest X-ray stage			
I	4	3	
II	14	16	
III	16	14	
0	2	3	
^{67}Ga lung scan (score)	1·75 ± 0·15	1·39 ± 0·15	n.s.
FVC (% predicted)	87·1 ± 2·8	82·6 ± 2·8	n.s.
FEV_1 (% predicted)	84·3 ± 3·0	80·9 ± 3·0	n.s.
*D*LCO (% predicted)	77·7 ± 3·8	81·0 ± 3·6	n.s.
PaO_2 (mmHg) ($n=30$ *vs* 30)	84·5 ± 1·6	85·5 ± 1·6	n.s.
S-ACE ($U\ l^{-1}$)	127·6 ± 9·3	128·5 ± 9·1	n.s.
Serum calcium ($mg\ dl^{-1}$)	9·6 ± 0·1	9·6 ± 0·1	n.s.
Urinary calcium (mg per 24 h)	270·1 ± 28·3	344·8 ± 27·5	n.s.

n.s., not significant, FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; *D*LCO, alveolar diffusion; PaO_2, arterial oxygen tension; S-ACE, serum angiotensin converting enzyme.

TABLE 4. Trial duration and mean daily doses of corticosteroids in the whole period and during each year from trial's beginning

	Deflazacort	Prednisone
Duration (months, mean ± SD)	42·0 ± 18·7	31·7 ± 17·7
Mean (± SD) daily dose, mg		
Whole period (n=36 *vs* 36)	14·8 ± 9·6	10·4 ± 6·1
First year(n=36 *vs*33)	21·5 ± 9·5	14·4 ± 7·6
Second year (n=31 *vs* 28)	15·4 ± 9·9	11·6 ± 5·8
Third year (n=27 *vs* 19)	9·7 ± 5·1	7·3 ± 6·1
Fourth year (n=14 *vs* 10)	9·3 ± 5·8	8·6 ± 5·7

Table 4 shows the trial duration and the mean daily doses of corticosteroids used during the whole trial and during each year. Sixty-nine patients completed 1 yr of trial, 59 patients completed 2 yr, 46 patients completed 3 yr, and 24 patients completed 4 yr or more (up to 7 yr). The mean duration (± SE) of the trial was 3·5 ± 1·56 in the DFZ and 2·6 ± 1·48 yr in the PDN group. Daily starting doses of corticosteroids (mean ± SD) were 22·3 ± 6·9 mg for PDN and 23·2 ± 11·4 mg for DFZ. The doses were progressively reduced from the first to the fourth year of therapy, and the drugs could be stopped in 19 patients. Mean daily doses from the start of the trial to the last record were 10·4 ± 6·1 mg PDN and 14·8 ± 9·6 mg DFZ.

Compliance was generally good, with few exceptions (see later). Sixteen patients (11 PDN, five DFZ) were lost to follow-up: three (all PDN) during the first year; 10 (five per group) during the second year, and one each during the third, fourth and fifth years (all PDN). The reasons were unknown for five patients (three DFZ, two PDN), four patients moved to another region (one DFZ, three PDN), three patients were uncooperative or had poor compliance (all PDN), one patient had transport problems (DFZ: the patient with bilateral optic nerve atrophy was blind), one patient had family problems (divorce) (PDN), and two patients stopped because of fear of side-effects (both PDN). Four further patients, all in the PDN group, interrupted the trial because of side-effects, three during the third year and one during the fourth year (see later); two were shifted to DFZ, which was well tolerated and is still being given, and the other two are still without therapy.

In 19 patients (12 DFZ, seven PDN), therapy was stopped because it was judged to be no longer necessary: four patients (three DFZ, one PDN) during the third year, 10 patients (five per group) during the fourth year, four patients (all DFZ) during the fifth year, and one patient (PDN) during the seventh year. All these patients are still being followed-up, and two patients (one per group) have been given therapy again because of relapse. Thirty-three patients (or 37 including the two patients who restarted therapy and the two patients shifted from PDN to DFZ) were still under therapy in December 1994, when the trial was closed in five patients (one DFZ, four PDN) after more than 2 yr, 10 patients (eight DFZ, two PDN) after more than 3 yr, and 18 patients (10 DFZ, eight PDN) after more than 4 yr. When the trial was closed, current daily doses ranged from 6 to 18 mg DFZ and from 5 to 20 mg PDN.

While drug-related adverse events are described (see later) for the total duration of the trial, the yearly results are statistically analysed only for the first 4 yr in view of the small number of patients followed-up for more than 4 yr.

The results regarding sarcoid activity parameters indicate a good response to treatment. Chest X-ray showed complete recovery in 26 patients (13 per group), and good improvement in 30 (15 per group). At final record, it was unchanged from baseline in eight patients (five DFZ, three PDN) and worse in two (one per group). It remained Stage 0 throughout the trial in five patients (two DFZ, three PDN), and could not be verified in one patient because of early drop out. ^{67}Gallium improvements are shown in Fig. 1. The score dropped significantly in 4 yr treatment in both groups: DFZ from 1·75 ± 0·15 to 1·10 ± 0·23, P<0·05; and PDN from 1·39 ± 0·15 to 0·53 ± 0·32, P=0·05. The decrease was even more striking in the first year of treatment, when the corticosteroid dose was higher; the improvement was similar in the two groups, with no significant difference (P>0·05). Angiotensin converting enzyme profiles (Fig. 2) also showed significant improvements with both drugs, without any significant difference between the two groups. Calciuria dropped from the recruitment values set out in Table 3 to 186·6 ± 47·1 (P<0·05) in the PDN group and 207·4 ± 39·9 in the DFZ group, after

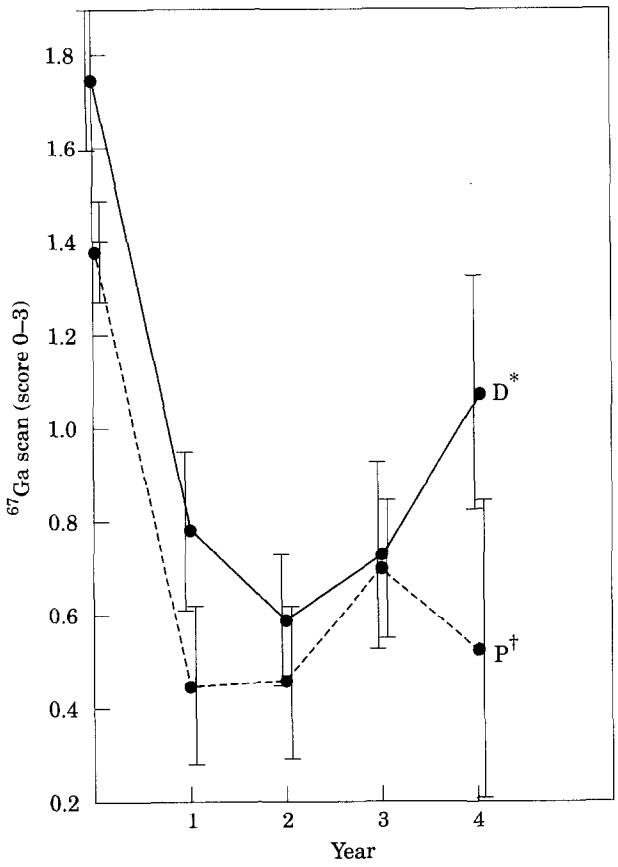

FIG. 1. Time course of ^{67}Ga lung scan score (mean ± SE. – – –, prednisone; ——, deflazacort. *P<0·05 *vs* baseline, †P=0·05 *vs* baseline. The number of patients at the end of each year is shown in Table 4.

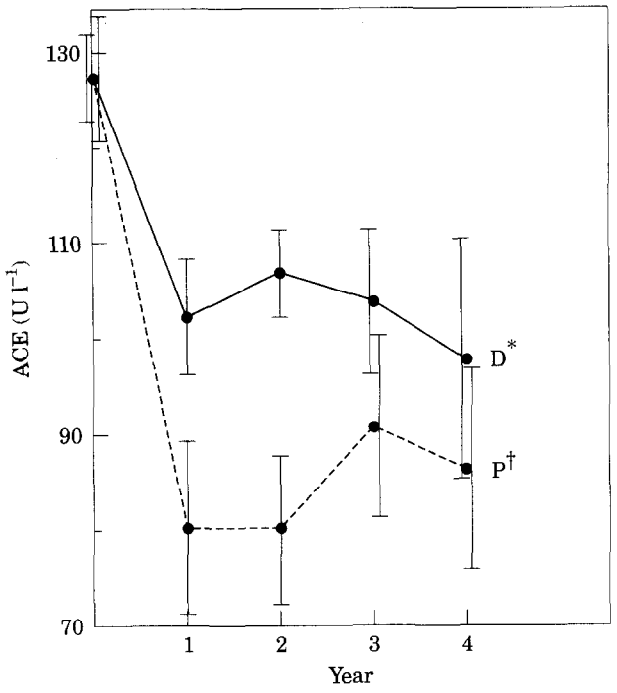

FIG. 2. Time course of serum angiotensin converting enzyme (ACE) (mean ± SE) (normal values: 34–125 U l^{-1}) – – –, prednisone; ——, deflazacort. *P<0·05 *vs* baseline, † P<0·01 *vs* baseline. The number of patients at the end of each year is shown in Table 4.

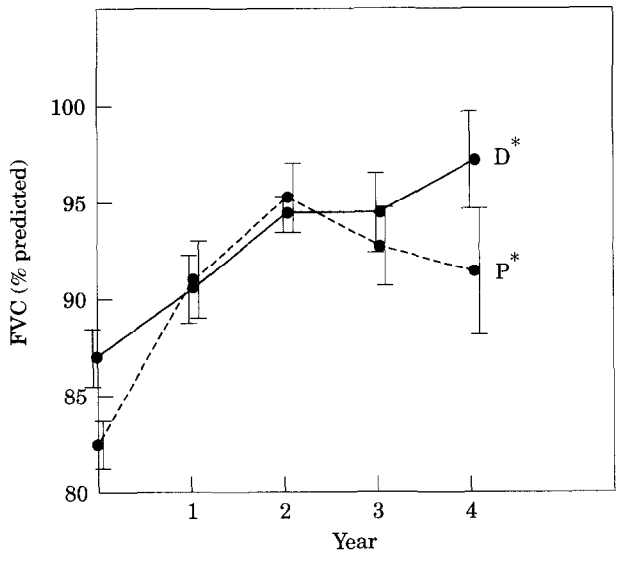

FIG. 3. Time course of forced vital capacity (FVC) (mean ± SE). – – –, prednisone; ——, deflazacort. *P<0·01 *vs* baseline. The number of patients at the end of each year is shown in Table 4.

4 yr of therapy. The FVC profiles are described in Fig. 3: the improvement was significant (P<0·01) with both drugs. FEV_1 reached 87·8 ± 2·4% predicted in the DFZ group, and 84·4 ± 2·7% in the PDN group after 4 yr of therapy; these differences from basal values were not significant. D_LCO improved, though also not significantly, after 1 yr to 85·7 ± 3·3% predicted in the DFZ group, and 93·1 ± 3·1% in the PDN group; the values remained good, although lower, after 4 yr, when the dose was lower, averaging 82·9 ± 4·0 in the DFZ group, and 83·9 ± 4·9 with PDN. PaO_2 changes from baseline were not significant over the years: PaO_2 averaged 85·8 ± 2·1 mmHg in the DFZ group at the end of the trial and 82·1 ± 2·6 in the PDN group. No changes were observed in serum calcium, which was normal at baseline in all cases.

The only significant changes in haematological or biochemical parameters, and in body weight, are shown in Table 5. In spite of these changes, the only significant difference between the two groups was in body weight, which increased significantly in the PDN group as compared to the DFZ group (P<0·01). Heart rate and systolic or diastolic blood pressure changes were unremarkable in both groups;

TABLE 5. Time-course profiles of body weight and haematological and biochemical parameters

Parameter	Baseline	First year	Second year	Third year	Fourth year	*P*
Body weight						
DFZ	70·1 ± 0·4	72·1 ± 0·5	71·8 ± 0·4	69·9 ± 0·6	70·0 ± 0·6	0·202
PDN	69·9 ± 0·4	72·0 ± 0·5	73·4 ± 0·5	72·2 ± 0·5	73·6 ± 0·8	0·001
Blood lymphocytes ($10^3\ \mu l^{-1}$)						
DFZ	1·88 ± 0·08	1·92 ± 0·09	1·94 ± 0·09	1·87 ± 0·11	2·30 ± 0·14	0·040
PDN	1·81 ± 0·08	1·96 ± 0·10	1·91 ± 0·10	2·24 ± 0·11	2·13 ± 0·18	0·039
Serum sodium (mmol l^{-1})						
DFZ	140·3 ± 0·6	139·4 ± 0·6	139·8 ± 0·6	140·2 ± 0·7	142·5 ± 0·9	0·040
PDN	139·0 ± 0·6	140·5 ± 0·6	140·3 ± 0·7	140·7 ± 0·9	139·4 ± 1·3	0·768
Serum potassium (mmol l^{-1})						
DFZ	4·39 ± 0·05	4·23 ± 0·05	4·13 ± 0·05	4·03 ± 0·07	4·15 ± 0·08	0·003
PDN	4·44 ± 0·05	4·06 ± 0·05	3·93 ± 0·06	4·05 ± 0·08	4·04 ± 0·11	0·005

DFZ, deflazacort; PDN, prednisone.
Values expressed as least squares mean ± within individual SE.
P denotes the probability for the hypothesis of no increasing or decreasing trend from trial's start to the fourth year of therapy (in each treatment group).

blood pressure rose above the upper threshold (140/90) in two DFZ patients and in three PDN patients.

Table 6 shows the drug-related adverse events that first occurred or worsened after starting therapy. The only severe side-effects were two episodes of pneumonia (DFZ) and one case of melena (PDN). One PDN patient had bilateral posterior subcapsular cataract and underwent bilateral lens implantation, and two DFZ patients had posterior cataract; nobody had visual loss.

The timing of drug-related adverse events differed, with most of the metabolic and nutritional side-effects

TABLE 6. Drug-related adverse events

	Deflazacort	Prednisone
n	36	36
Metabolic and nutritional (weight gain, facies lunaris, abdomen striae, face hypertrichosis, Na or K disorders)	15	25
Gastrointestinal tract disorders (dyspepsia, gastritis, abdominal pain, melena)	4	9
Hypertension	2	3
Serious infections (pneumonia)	2	0
Limb oedema	0	2
Diabetes (hyperglycemia >140 mg dl^{-1}, glycosuria)	3	2
Reproductive system (amenorrhea, dismenorrhea, menorrhagia, loss of libido)	1	2
Cataract	2	1
Nervousness	0	1
Bone fractures	1	6
Bone pain	2	10

appearing in the first months of therapy, whereas cataract and skeletal disorders (see later) were late complications. Cataract appeared after 2 yr of PDN therapy in the patient who underwent bilateral lens implantation, and after 3 yr of DFZ therapy in two. All but one of the fractures occurred 3–5 yr after beginning therapy, in spite of the well-known early drop of BMC in the first months of corticosteroid therapy.

Four drug-related drop-outs due to side-effects were reported in the PDN group, all more than 2 yr after beginning therapy. The causes were bone pain, accompanied by a severe reduction of BMC in two, dyspepsia in one, and body weight gain (11 kg) in one; two of these four patients were shifted to DFZ, which was tolerated better and is still being given to both.

BONE TOXICITY ANALYSIS

Of the 36 patients enrolled in each treatment group, five given DFZ and eight given PDN were not evaluable for bone toxicity analysis, since they had only one or two QCT assessments. One other DFZ patient was excluded because she underwent hysterectomy 6 months after the study started. To sum up, 30 patients in the DFZ group and 28 in the PDN group met the requirements for analysis of bone mass loss. Their demographic and clinical characteristics at recruitment were well matched in the two groups with no noteworthy differences with regard to age, sex, body weight, postmenopausal status, pulmonary and extrapulmonary involvement, radiological stage, duration of disease and initial VCMC.

Limiting the observation to the above patients, the trial lasted 32·4 ± 8·7 (SD) months (DFZ group) and 31·6 ± 8·5 months (PDN group); the range for both groups was 2–6 yr. The mean daily dose during each year from the start to the fourth year was similar to that shown in Table 4 for the whole group of patients. The dose decreased progressively in both groups year by year, and the dose ratio DFZ:PDN (mg/mg) ranged from 0·96 at the second year to 1·35 at the third year, thus confirming that the doses of DFZ and PDN had been titrated in order to obtain the same desired therapeutic response.

At the end of the trial, 21 patients (12 DFZ, nine PDN) are no longer taking corticosteroids. The others are taking a daily maintenance dose of 7·9 ± 2·9 mg of DFZ (18 patients) or 9·3 ± 4·6 mg of PDN (19 patients), and will probably be continuing this treatment for a long time yet. With this dose, they are under control with stability or improvement of symptoms and of the most important parameters.

Figure 4 shows the average bone mass loss curves for DFZ and PDN together with the average

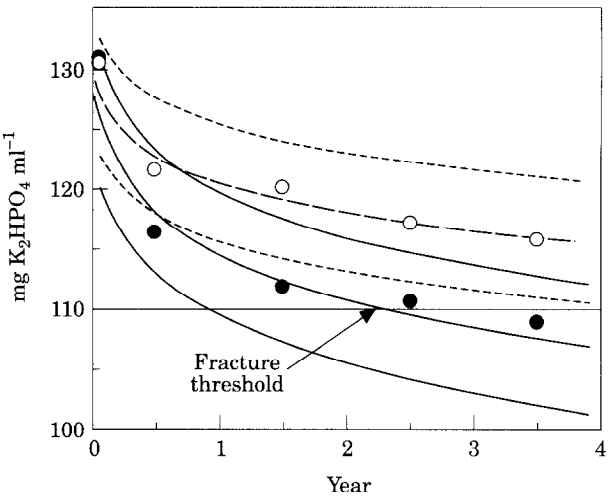

FIG. 4. Mean VCMC loss (mg K_2HPO_4 ml^{-1}) for deflazacort (– – –) and prednisone (——) ± SE (· · · ·), and mean residuals (○, ●). The difference between the two curves is statistically significant (P=0·033). The horizontal line at the level of 110 mg K_2HPO_4 eq represents the fracture threshold (38).

residuals from the individual curves. Mean residuals are lower than 2% of the fitted values, indicating that the bone mass loss model fits observed data satisfactorily. During the 4 yr under study, BMC dropped from 129·8 ± 5·6 mg K_2HPO_4 ml^{-1} to 106·7 ± 5·4 in the PDN group, and from 130·2 ± 4·8 to 115·6 ± 5·2 in the DFZ group. This implies a mean loss of 18 (PDN) *vs* 11% (DFZ); P<0·05.

The mean VCMC loss velocity per year was about 1·6 times higher in the PDN than the DFZ group (P<0·05) (Table 7). VCMC loss velocity was decreased from the beginning to the end of the trial; from about − 5·5 ± 0·7 mg K_2HPO_4 ml^{-1} yr^{-1} in PDN group and − 3·4 ± 0·6 in DFZ group at the end of the first year of treatment, to only − 1·4 ± 0·32 in the PDN group and − 0·9 ± 0·2 in the DFZ group at the end of the fourth year.

VCMC loss velocity was significantly higher with higher glucocorticoid doses (P<0·01) (Fig. 5) and

TABLE 7. Mean VCMC loss velocity* at the end of the first 4 y therapy

Year	Deflazacort	Prednisone
1	− 3·45 ± 0·60	− 5·48 ± 0·71
2	− 1·79 ± 0·31	− 2·85 ± 0·37
3	− 1·21 ± 0·21	− 1·92 ± 0·25
4	− 0·92 ± 0·16	− 1·45 ± 0·19

*mg K_2HPO_4 ml^{-1} yr^{-1}, mean ± SE.

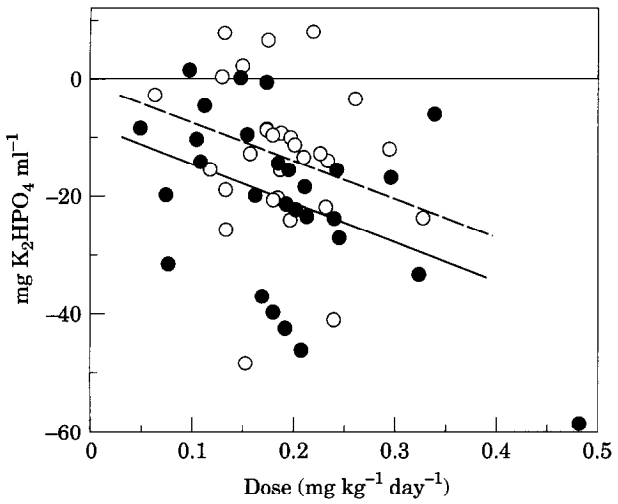

FIG. 5. Scatterplot and regression lines of VCMC loss (mg K_2HPO_4 ml^{-1}) *vs* mean daily dose (mg day^{-1} kg^{-1} of body weight) over the whole study. ●, ——, prednisone. ○, – – –, deflazacort. The slope of both regression lines is significant at 0·01 level. Mean VCMC loss (adjusted for doses) is significantly different between groups ($P<0·05$).

bone toxicity tended to be higher in PDN than in DFZ patients ($P<0·05$). Twelve patients in the PDN group and only six in the DFZ group had bone mass loss higher than 20 mg K_2HPO_4 ml^{-1}.

In addition, the occurrence rate of skeletal fractures from minimal trauma was six events (rib, epitrochlear, two vertebral crush and two vertebral wedge fractures) in five PDN-treated patients (one with two wedge fractures) and one event (vertebral crush fracture) in one DFZ-treated patient. All but one of the fractures occurred after 3 or more years of therapy, in agreement with the shape of the PDN curve in Figure 4; while the DFZ curve (mean − SE) remains above the level of 110 mg K_2HPO_4 ml^{-1}, which is considered the fracture threshold (24), the mean PDN curve goes below the threshold after 2·3 yr of therapy, suggesting that after that time, a number of fractures are to be expected, mainly in the PDN group. Three of the six patients with fractures had a *z*-score near to − 2 at recruitment.

Light to severe bone pain was reported in 10 PDN and two DFZ patients, in addition to those who developed skeletal fractures, and eight PDN *vs* two DFZ patients had to start corrective measures (bisphosphonates, calcitonin or oestrogens) for their bone loss.

Discussion

Chronic PDN at a daily dose of 5–15 mg is associated with serious adverse effects (25,26), and therapy will probably be required for life by many patients with sarcoidosis. In such a situation, the search for a corticosteroid with lower side-effects is of major interest.

These results confirm that the efficacy of DFZ is comparable to that of PDN. Similar results were found in a 6-month trial (8). This has also been observed in other diseases over periods ranging from 12 to 15 months (1–4). In this trial, some rebound to positivity in the ^{67}Ga scan profile may be observed after the second year (Fig. 1, DFZ curve); similarly, a small drop in *D*LCO was observed after the third year. The reason probably lies in the reduction of corticosteroid dosage over the years which permitted the sarcoid activity to reemerge. However, the authors' aim was not so much to improve the ^{67}Ga images as to preserve respiratory function, and in fact FVC and *D*LCO did remain at acceptable levels. A second reason may be that only severely impaired patients are willing to comply with frequent tests over a long period, so that there may be some selection of the most severely diseased patients.

As regards safety, haematological and biochemical variables did not show clinically important changes in either group, but most patients had drug-related adverse events, more frequent in the PDN group. Since there are no other reports of controlled trials longer than 15 months for DFZ, there were no terms of comparison. However, these results are in agreement both with the better safety of DFZ than PDN observed in shorter, double-blind trials (2–4) and with the authors' previous study on DFZ (7).

The most frequent side-effect was weight gain, reported by 19 of the 72 patients (26·3%). A similar observation was described by Johns (27), who noted weight gain in 24% of a series of 171 sarcoid patients with mean PDN treatment of eight years. Patients dropped out on account of adverse events in the PDN group alone.

The most disabling adverse event was skeletal fractures. Generally, corticosteroids indirectly affect bone mass by reducing gastrointestinal calcium absorption thereby increasing parathyroid hormone activity (28). The present findings are in good agreement with those indicating that bone loss occurs rapidly, within the first 6–12 months of glucocorticoid therapy, after which the rate of bone mass loss declines more slowly (29,30). Atraumatic fractures did not occur until after 2 or more years of therapy, when mean VCMC dropped below the atraumatic fracture threshold. Similarly, Adinoff and Hollister (31) reported that all their asthmatic patients with fractures had received prednisone for at least 3 yr before the first fracture.

These data confirm that a low initial VCMC is an important risk factor for fractures; reduced bone

mineral density was the strongest predictor for fractures in other studies too (17,32). It is now known that it is probably wise to protect patients with an initial z-score of $-1{\cdot}5$ or less and needing steroids with corrective measures, avoiding their inclusion in this trial. However, this was not so clear when the trial was started in 1987.

Prospective longitudinal studies are few, but these data (mineral loss 11% in the DFZ group *vs* 18% in the PDN group during 4 yr of treatment) are in agreement with published reports. As regards the effects of steroid doses and treatment duration on the extent of bone mass loss, data are contradictory mainly because the range of doses administered may be too narrow and the duration of treatment too short to detect any consistent relationship with bone mass loss. In the present trial, mean daily doses are fairly evenly scattered between 0·05 and 0·35 mg kg^{-1} day^{-1}, and treatment duration ranged uniformly between 18 and 48 months. Therefore, this study formed a definite correlation between dose and VCMC loss (Fig. 5) despite the wide intra- and inter-individual variability.

However, vertebral mineral density loss was significantly ($P<0{\cdot}05$) greater in the PDN than the DFZ group over the whole period of treatment.

The bone loss indicated a constant bone toxicity ratio, PDN:DFZ of about 1·6. The higher bone toxicity of PDN emerges both at low and high doses. After 3 yr continuous treatment, both bone loss and atraumatic fractures were more evident in patients treated with PDN (six events in five patients) than in patients treated with DFZ (one case). Moreover, the mean curve of DFZ, unlike the PDN one, did not reach the fracture threshold during the trial. This suggests that the lower rate of bone loss during treatment with DFZ may lower the risk of spontaneous fractures.

In conclusion, this trial confirms the comparable efficacy of DFZ and PDN in the long-term therapy of chronic sarcoidosis. Skeletal, metabolic, nutritional and gastrointestinal tract disorders appeared more frequently in PDN-treated patients.

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